Commentary on STOP DIABETES study

In this real-world observational, retrospective study, it was evaluated whether it was possible to stop the conversion of prediabetes to diabetes (Type 2) through lifestyle or pharmacological therapy. It was based on personalized interventions, and pathophysiology, beta-cell function, and glucose tolerance, were assessed. If the intervention improved beta-cell function, it was a strong predictor that prevention of progression from prediabetes to diabetes would happen. There are limitations of the study, but it showed that even people with normal glucose tolerance do progress to diabetes and should be a subgroup that needs intervention as they too are prediabetic, rather than assume that such patients will not progress, and only those with impaired glucose tolerance would progress. Compared with participants, who received lifestyle therapy only, progression to type 2 diabetes was significantly lesser in participants who received triple, rather than in those receiving dual, oral antidiabetic therapy. Improved beta-cell function was the strongest predictor of type 2 diabetes prevention. Whether these data are applicable to other populations is debatable. It is also debatable whether the results reflect the prevention or masking of diabetes through pharmacological treatment. Determining the contribution of each agent alone to the reduction in diabetes incidence is not possible. Finally, the lifestyle intervention was not as rigorous as practiced in the Diabetes Prevention Project.

It is a good article though there will be limitations because of its retrospective, observational nature, and perhaps it may not represent a paradigm shift, but the hope is that it will stimulate thinking in this direction.[1] Can we stop the progression of prediabetes to diabetes? The fact that a real-world, pathophysiology-based therapeutic approach in a community practice setting could prevent the development of type 2 diabetes in high-risk individuals, is an important consideration and gives one food for thought.

If we look at the Kaplan–Meier curve, most patients have been followed up for up to 20 months only. Rather than progression to diabetes (which is merely a continuum of this metabolic disease), it would be meaningful to look at better endpoints such as all-cause mortality, cardiovascular (CV) mortality, or quality of life (QoL), in a Steno-2 or the United Kingdom Prospective Diabetes Study-like study design.

This STOP DIABETES study generates a hypothesis that we can start metabolic pharmacotherapy in the prediabetic stage, rather than in frank diabetes. However, the hard outcomes of such an approach, as compared to starting pharmacotherapy after diabetes onset, need to be proven in long-term study designs. Progression to diabetes may not be as good as the other endpoints like survival, because there may be regression to the mean of early benefits over the long-term.

The body has a tendency to develop tolerance to pharmacological effects of the drugs. While we are delaying diabetes at an early stage using pharmacological interventions, for how long would the pharmacological benefits be available? Will it also have an adverse influence on lifestyle interventions which are the mainstay in prediabetes? All these things can be answered from assessing the overall survival and QoL in the long-term.

Having said this, we need to understand that prediabetes is also fraught with risk of CV disease.[2] So should the goal glycated hemoglobin (HbA1c) for prediabetics be 5.6%? Just as it is 6.5% for diabetics?

Furthermore, not all prediabetics progress to diabetes. Those whose fasting plasma glucose is between 115 and 125 mg/dl, and whose postprandial plasma glucose is between 180 and 199 mg/dl, and those who are overweight or obese and have a family history of diabetes with premature coronary artery disease are the ones who are most likely to progress (one-third).

So selecting them in any 3-year prospective trial (followed by 1 year off drug to evaluate durability or sustainability), evaluating a treatment for prediabetics increases the probability of success. One-third of prediabetics do not progress, and one-third are well controlled with metformin and lifestyle modification. The rate of conversion from prediabetes to diabetes in India is the highest at 18%–19%.[3]

Diet (appropriate partial or full meal replacement in consultation with a dietician) needs to be prescribed and so does exercise. Only then will they be followed by patients,

the way they are adherent to drugs. For the initial weight loss, dietary control is better (calorie restriction), but later for maintenance of the lost weight, exercise is better. In addition, depending on the macronutrients (amount and frequency) we eat (carbohydrate, protein, and fat) one will have a differential insulin response.

This article has important implications for Indians with diabetes. Diet and exercise (lifestyle modification) are as important, if not more important than drugs and in any case, should precede the use of drugs (if patients are picked up early). If well motivated, they can make a vast difference to the management of diabetes, not only just in terms of preventing conversion of prediabetes to diabetes, but also in halting progression of obesity to diabetes, and diabetes to complications of uncontrolled diabetes (such as ischemic heart disease), and perhaps even in reversing diabetes in select cases. Somehow, it is difficult to believe that diabetes can ever be cured. At best, it can be controlled, its inexorable progression may be halted, regression may happen, but only as long as one strictly adheres to lifestyle modification advice.

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Conflicts of interest

There are no conflicts of interest.

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REFERENCES

1. Armato JP, DeFronzo RA, AbdulGhani M, Ruby RJ. Successful treatment of prediabetes in clinical practice using physiological assessment (STOP DIABETES). Lancet Diabetes Endocrinol 2018;6:781-9.
2. Vas PR, Alberti KG, Edmonds ME. Prediabetes: Moving away from a glucocentric definition. Lancet Diabetes Endocrinol 2017;5:848-9.
3. Dutta D, Mondal SA, Choudhuri S, Maisnam I, Hasanoor Reza AH, Bhattacharya B, *et al.* Vitamin-D supplementation in prediabetes reduced progression to type 2 diabetes and was associated with decreased insulin resistance and systemic inflammation: An open label randomized prospective study from Eastern India. Diabetes Res Clin Pract 2014;103:e18-23.

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